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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,711	04/17/2001	Stephen G. Withers	UBC. P-005 - 2	1131

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,711	WITHERS ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-50 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-50 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 30, 2004 has been entered.

The amendment filed August 30, 2004 amending claim 40 has been entered.

Claims 40-50 and 55 are pending.

Response to Amendment

The Declaration under 37 CFR 1.132 by Dr. Stephen Withers filed August 30, 2004 is insufficient to overcome the 112, 1st paragraph, enablement rejection of claims 40-50 and 55 as set forth in the last Office action because: the Declaration concerns with "modified glycosyl donor molecule" and "glycoside acceptor molecule" and asserts that not only monosaccharide fluorides but also other leaving groups are enabled (pages 6-8). It is noted that the claims are not limited to monosaccharide donors containing small leaving groups such that to allow that donor molecule to fit within the active site of the mutant glycosidase.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-50 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for synthesizing an oligosaccharide by coupling a modified glycosyl donor molecule and a glycoside acceptor molecule using a mutant form of glycosidase enzyme, said enzyme being selected from among glycosidase enzymes having two catalytically active amino acids with carboxylic acid side chains within the active site of the wild-type enzyme, said mutant enzyme being mutated to replace one of said catalytically active amino acids having a carboxylic acid side chain with a different amino acid of smaller size. Claims are further limited to retaining and inverting glycosidases (claim 41, with dependent claims 42-49, and claim 50, respectively).

Therefore, the claims are drawn to a method of making of a genus of oligosaccharides comprising any number of monosaccharides joined by any glycosidic linkages i.e., 1-2, 1-3, 1-4 or 1-6 and any stereo configuration, i.e. α or β. The starting material encompasses any glycosyl donor molecule and any glycoside acceptor molecule, said molecules coupled by the mutant glycosidase "that corresponds to the

donor molecule and the acceptor molecule to be coupled". The specification teaches the use of α–galactosyl fluoride and α-glucosyl fluoride, i.e. monosaccharides as donor molecules and aryl-glucosides as acceptor molecules (Tables 1-4). In each case β-1,4 linked disaccharide was formed and sometimes β-1,3 link (Table 2) and trisaccharides and tetrasaccharides were formed as well (Tables 2, 4). The specification fails to teach the correlation between the composition, stereo- and regio- specificity of donor and acceptor molecules and the oligosaccharide to be made. With regard to the genus of mutant glycosidases, it encompasses not only naturally–occurring but also man made structures that are structurally limited only by the presence of two catalytically active carboxylic residues. The genus of glycosidase encompasses enzymes with different structures and functions. The naturally occurring glycosidase are grouped in over 80 families comprising endo- and exo-glycosidases with different substrate, stereo- and regio- specificity. Said glycosidases encompass retaining as well as inverting enzymes. The specification teaches only a single representative species, Abg (a retaining β-1, 4 glucosidase from *Agrobacterium faecalis*) that is mutated at the active site nucleophile Glu358Ala. Thus, the scope of the claims includes numerous structural variants, and the genera of glycosidases, donor and acceptor molecules are highly variant because a significant number of structural differences between genus members is permitted.

Given this lack of description of representative species encompassed by the genera of the oligosaccharides to be made, donor, acceptor and glycosidase molecules, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 40-50 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of retaining glycosidases wherein the catalytically active nucleophilic carboxylic acid is substituted with a non-nucleophilic residue of equal of smaller size to form an oligosaccharide using a specific glycosyl monosaccharide of opposite anomeric configuration to the wild-type enzyme's substrate as a donor, said donor containing a small leaving group, and a specific acceptor, does not reasonably provide enablement for a method for synthesizing any oligosaccharide using any glycosidase and any donor and acceptor molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claims 40-50 and 55 are so broad as to encompass method of use of any glycosidase both retaining and inverting, in which any one of the two catalytic carboxylic amino acids is mutated, in a stereospecific reaction using any donor and acceptor. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glycosidases having different structures, functions and substrate specificities, and donors and acceptors broadly encompassed by the claims. The disclosure teaches the method of use of a retaining glucosidase mutant, AbgE358A, with α-glucosyl fluoride or α-galactosyl fluoride as a donor and arylglycosides as acceptors to form oligosaccharides (Tables 1-4). The Declaration under 37 CFR 1.132 by Dr. Withers filed June 3, 2002 teaches the use of a nucleophile mutant of another retaining glycosidase, *E. coli* LacZ β-galactosidase, with a-galactosyl fluoride as a donor and two acceptors to form oligosaccharides. Therefore, only monosaccharides, i.e. α-glucosyl fluoride and α-galactosyl fluoride are used as a donor. The art published after the filing date of the instant application teaches a few examples of other retaining glycosidases mutated at a catalytically active carboxylic acid nucleophile with a respective glycosyl fluoride as a donor. Thus, no donors other than a respective glycosyl fluoride and a limited number of acceptors are known to be used up to date. However, the claims encompass any donor-acceptor pair irrespectively of the original substrate specificity of a glycosidase. Therefore, based on the instant

disclosure and the state of the art, it is unpredictable whether any glycosidase when mutated at any one of the two catalytically active carboxylic amino acids will catalyze coupling of any glycosyl donor and any glycoside acceptor having opposite stereochemical configurations by either inverting or retaining mechanism.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use any mutant glycosidase with any donor and any acceptor other than a retaining glycosidase mutated at a nucleophile catalytically active carboxylic acid with a respective glycosyl fluoride and acceptor to form an oligosaccharide in a manner reasonably correlated with the scope of the claims.

Without sufficient guidance, using any mutant glycosidase with any donor other than glycosyl monosaccharide containing a small leaving group and any acceptor is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-50 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 (claims 41-50 and 55 dependent thereon) has been amended to recite "modified glycosyl donor" (emphasis added). Said term is defined in the specification by

non-limiting examples rendering the metes and bounds of the claims unascertainable (page 8, line 19; page 12, lines 3-11).

Furthermore, claim 40 recites "the wild-type enzyme that corresponds to the donor molecule and the acceptor molecule to be coupled". The specification does not define what renders the enzyme corresponding to the donor and acceptor molecules.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40-50 and 55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,716,812. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming common subject matter, as follows: a method of coupling a glycosyl donor and a glycoside acceptor having opposite stereochemical configurations using a mutant glycosidase.

Claims 40-50 and 55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,284,494. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming common subject matter, as follows: a method of coupling a glycosyl donor and a glycoside acceptor having opposite stereochemical configurations using the *Agrobacterium* β-glucosidase E358A mutant as defined in claims 1 and 2 of U.S. Patent No. 6,284,494.

Applicant's consideration for filing a TD stated in Responses filed June 3, 2002, March 4, 2003, November 24, 2003 and the current Remarks (page 11) is noted. The rejections are maintained until TD is filed.

Response to Arguments

Applicants' arguments filed on August 30, 2004 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, rejection, Applicants argue that the specification "broadly teaches the mutation of a glycosidase, both retaining and inverting, at one of two catalytically active amino acids in the active site of the enzyme to result in an enzyme that has lost the ability to hydrolyze oligosaccharide products, but that retain the ability to couple corresponding donor and acceptor molecules. Generally, the substrate specificity of the wild-type enzyme is retained" (Remarks, page 5). This is not persuasive because the claims are not limited to glycosidase that differ from

naturally occurring wild type enzyme by a mutated nucleophilic carboxylic acid. The claims further are not limited to specific donor and acceptor molecules as discussed above. In addition, the claims are drawn to a method of making an oligosaccharide product not to a mutant glycosidase, and the assertion that "Generally, the substrate specificity of the wild-type enzyme is retained" does not render the method enabled and the oligosaccharide p[product to be made described. Applicants further discuss Dr. Withers' Declaration (pages 6-8). As noted above, the instant claims do not limit the donor molecules to glycosyl monosaccharides of opposite anomeric configuration to the wild-type enzyme's substrate as a donor, said donor containing a small leaving group such that to allow that donor molecule to fit within the active site of the mutant glycosidase.

Applicants further argue that "It is well settled that a working example is not required of the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation" (page 9). This is agreed with. the claims are not enabled because the specification lacks working examples but because the claims encompass inventions other than described and enabled.

With regard to the 112, 2nd paragraph, rejection Applicants argue that the amendment obviates the rejection. The rejection was reworded to explain the examiner's position. Applicants argue that "Some difference in substrate specificity, either more limited or more expanded, would be expected depending on the size of the amino acid residue substituted for the catalytically active amino acid having the carboxylic acid side chain, but this variation would not be sufficient to render the term

["modified"] indefinite" (page 10). This is not persuasive because the "leaving" group does not change the substrate specificity, i.e. specificity to saccharide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

November 10, 2004